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Directly observed Rivaroxaban therapy for recurrent venous thromboembolism integrated into methadone maintenance. A case report.

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Summary

Background: Intravenous drug use is associated with venous thromboembolism and poor compliance with medication. This puts patients at risk of recurrence of a potentially life-threatening disease and creates a significant challenge for clinicians. In the same patient group, adherence to treatment for HIV, hepatitis c, and tuberculosis improves when combined with methadone maintenance and in directly observed therapy but this approach is generally not employed in the management of other conditions. **Case Report:** A drug user, with a history of thrombophilia and repeated thromboembolism, presented with a recurrence of pulmonary embolism after not adhering to anticoagulation. Rivaroxaban was restarted in directly observed therapy, combined with the already established methadone therapy. This led to compliance with anticoagulation without affecting the stabilisation treatment. **Conclusions:** This strategy, mainly used to improve compliance in the management of conditions that pose a particular risk to public health, should be considered to help drug users adhere to therapy for venous thromboembolism and indeed other medical conditions. This is the first published case where anticoagulation has been successfully integrated into directly observed methadone maintenance.

Key Words: Drug Dependence; Medication Adherence; Venous and Pulmonary Embolism; Directly observed therapy; Agonist Opioid Treatment; Methadone; Anticoagulation

1. Introduction

Venous thromboembolism is a potentially life threatening disease. Intravenous drug use is a significant risk factor [7]. Injection into the groin has been reported as the single most frequent cause for a deep vein thrombosis (DVT) in female patients up to the age of 40 [22]. The risk is also particularly high in HIV positive patients that inject drugs [29]. The prevalence of DVT has been estimated to be as high as 13.9% with an annual incidence of 3.2% [8]. Both septic and non-infected pulmonary emboli have been described in intravenous drug users [15, 16]. Addiction is associated with poor adherence to medication which results in periods of subtherapeutic anticoagulation and risk of recurrence [30].

Users of intravenous drugs have a significantly increased mortality [21]. Strategies have been developed to improve adherence to medications, mainly in conditions that bear a risk to public health, whilst at the same time trying to reintegrate problem drug users into society.

Methadone was first synthesized in the late 1930s by Max Bockmühl and Gustav Ehrhart [3]. It is used as a racemic mixture. The R-enantiomer is a μ-opioid receptor agonist, while both isomers also act antagonistic on NMDA receptors [9, 10]. After oral administration, methadone undergoes a significant first pass metabolism with a large variation of bioavailabilty between individual patients. Methadone is metabolized in the liver by CYP3A4 and CYP2D6. Medications that inhibit or induce these enzymes will result in enhanced levels of methadone with increased risk of toxicity or decreased levels, leading to possible withdrawal and risk of relapse into substance misuse. Methadone itself is a moderate inhibitor of CYP3A4 and also inhibits CYP2D6 [4, 12].

Methadone maintenance treatment is a form of

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agonist opioid therapy. It has been widely used since the 1960s after it was evaluated as a response to the epidemic of narcotics addiction in New York City after the Second World War. Then, 75% of deaths in the 15-35 year age group were attributed to heroin use [14]. The establishment of methadone clinics resulted in a significant reduction in addiction-related crime, drug-arrests, hepatitis and mortality [17]. In the United States, more than 300,000 patients in opioid treatment programs receive methadone [31]. In the European Union, an estimated 700,000 users received agonist opioid treatment in 2013 where methadone is the therapy of choice in 69% of patients [11]. Patients on higher doses of methadone are more likely to continue with maintenance therapy [23].

Directly observed therapy is rooted in the treatment of tuberculosis in non-adherent patients. A health care worker or designated individual observes the patient swallow every dose of the prescribed drugs [18]. Combining methadone maintenance with antituberculous therapy or prophylaxis has aided adherence and completion of treatment [13]. Integrating HIV care into methadone maintenance has shown to improve the physical health of non-engaging HIV positive opioid dependent patients and improves adherence and viral load [19, 1]. This effect is not sustained after uncoupling methadone maintenance and antiretroviral treatments and it is suggested to continue the combined observed therapy long term [2]. Patients receiving higher doses of methadone are more likely to achieve ≥95% adherence to antiretroviral therapy than those receiving lower doses [20]. Hepatitis c treatment has been successfully integrated into methadone maintenance therapy [6]. This leads to greater success in starting treatment as well as higher early and sustained virologic responses compared to standard therapy [5].

Rivaroxaban is a direct factor Xa activator. It is licensed for the treatment of deep vein thrombosis and pulmonary embolism in the UK [26, 27]. The recommended dose is 15 mg twice daily for the first 21 days followed by 20 mg once daily thereafter. Dose reduction is necessary in patients with a reduced creatinine clearance. The drug has a high bioavailability of 80-100% [25]. The absorption is mediated by P-glycoprotein 1 and it is metabolized by CYP3A4. Rivaroxaban should be used with great caution if taken with medications that strongly inhibit or induce these. This includes antibiotics, like clarithromycin and rifampicin, "azole"-antimycotics (itraconazole, ketoconazole etc.), HIV protease inhibitors, antiepileptics (phenytoin, carbamazepine, phenobarbital), and St John's Wort [32]. For this reason, the drug may be unsuitable in patients undergoing treatment for tuberculosis or who are receiving anti-retroviral therapy. It has been reported, though, that Rivaroxaban can be administered safely in conjunction with substrates or moderate inhibitors of CYP3A4 and/or P-glycoprotein 1 without effect on its pharmacokinetic properties [24]. Rivaroxaban itself is not an inhibitor or inducer of any major CYP isoenzyme [25]. No interactions between methadone and Rivaroxaban have been reported in the literature. The anticoagulation effect of Rivaroxaban does not need monitoring. This is of advantage in patients with poor venous access or poor attendance to clinics, though, for patients on long term treatment it is recommended to measure renal function once yearly. The short half life of this drug and similar direct thrombin or factor Xa inhibitors leads to a rapid decline in the anticoagulant effect if doses are missed [28]. In patients with poor compliance this will increase the risk of recurrent thromboembolic events.

2. Case Report

A 38 year old male patient was diagnosed with recurrent pulmonary embolism to acute medical receiving after having been referred by his general practitioner with haemoptysis. He previously had suffered bilateral pulmonary emboli in December 2010 and an extensive right-sided deep vein thrombosis in January 2015. He was found to be heterozygous for factor V Leiden in 2011. His full blood count, coagulation and calculated creatinine clearance were within the reference range. His transaminases had been mildly elevated for a long time. In the past no cause had been found for this. Recent tests for HIV, hepatitis b and c were negative. There was no history of excessive alcohol use. He had no other significant past medical, surgical or psychiatric history. He was unemployed and lived with his elderly parents.

The patient had a long history of recreational drug use. For at least six years he had been fully established on methadone maintenance therapy, prescribed by the local branch of a national drug and alcohol network. He continued to occasionally take heroin, by intravenous injection but not into any groin or neck vessels. The patient was on oral methadone 90 mg once daily, but not any other regular medications.

His deep vein thrombosis in 2015 was his second definite thrombotic event on the background of thrombophilia. Because of the high risk of recurrence it was decided that he ought to be on lifelong anticoagulation. He was initially treated with self administered subcuta-

neous injections of Enoxaparin (1.5 mg/kg once daily) and then warfarin. Due to not attending regular blood tests to monitor his anticoagulation and to avoid long term injection of low molecular weight heparin, after consulting with the haematologists, he was started on the direct factor Xa activator Rivaroxaban in July 2015.

Despite understanding the risk of recurrent and potentially fatal thromboembolic events, the patient found it very difficult to adhere to his oral anticoagulation therapy. In fact, between July 2015 and the pulmonary embolism at the beginning of January 2016, he had only taken part of his initial three week medication starting pack. The patient was not able to report any specific reasons for his poor compliance.

It was then decided to give Rivaroxaban in directly observed therapy together with his methadone. The person responsible for supervising him in his methadone dosing would also observe the patient take his anticoagulation therapy, initially twice daily during the loading phase and then once a day.

In follow up interviews over the following three months, both the patient and the provider of the directly observed therapy independently confirmed that since combining methadone maintenance and anticoagulation, there has been very good adherence to the treatment throughout. No change in the perceived effect of methadone was reported. The patient and the therapy provider currently continue to be interviewed at regular intervals.

3. Conclusions

This is the first described attempt to combine anticoagulation in directly observed therapy with methadone maintenance. The same well established strategies that have been developed to improve adherence in the treatment of tuberculosis, HIV and hepatitis c can be used to aid in the treatment of venous thromboembolism and indeed other medical conditions. The approach may not be suitable for all and requires both motivated patients and addiction services. The choice of anticoagulant will depend on local policies and each individual patient. Observation of therapy by the provider of daily methadone maintenance ensures adherence whilst the patient is enrolled in this particular form of stabilisation therapy. Further research is necessary to investigate the general and long term feasibility of this approach.

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Ethics

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